UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/613,524	07/03/2003	Arthur M. Krieg	C1037.70042US00	4728

7590 06/27/2007

Maria A. Trevisan
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, MA 02210

EXAMINER	
OGUNBIYI, OLUWATOSIN A	
ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
06/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/613,524	KRIEG, ARTHUR M.	
	Examiner	Art Unit	
	Oluwatosin Ogunbiyi	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45 and 96-98* is/are pending in the application.

4a) Of the above claim(s) *12-15,40-42, 45 and 96-98* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *Claims 1-13, 16-39, 43 and 44 are rejected* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/29/04,10/27/2004, 12/8/2006,*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The originally filed claims filed 10/03/2003 and the amended claims filed 1/14/2004 were misnumbered. Claim 16 is absent from originally filed claims and amended claims. Accordingly, claims 17-99 have been renumbered 16-98 respectively (see 37 CFR 1.126). Applicant(s) next amendment to the claims should reflect these changes. Thus, claims 1-98 were originally filed. Claims 46-95 have been cancelled in the amendment filed 11/14/2004. Claims 1-45 and 96-98 are now pending in the application.

Election/Restrictions

Applicant's election of Group I claims 1-45 (now 1-44 due to renumbering) drawn to a composition comprising the nucleotide sequence of SEQ ID NO: 1 is acknowledged. The examiner inadvertently included claim 46 (now claim 45 due to renumbering) drawn to a method for stimulating an immune response in the claims of Group I. Claim 46 (now 5 due to renumbering) is not included in Group I and the Examiner apologizes for any confusion this may have caused and thanks Applicant for pointing out this discrepancy. Claim 46 (now 45 due to renumbering) is meant to be included in Group II.

Applicant's election of a viral antigen and an anti-viral medicament is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 12, 13, 14,15, 40-42, 45 and 96-98 (according to renumbering) are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and species there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed 5/7/2007.

Claims 1-13, 16-39, 43 and 44 (according to renumbering) are being examined as drawn to elected invention and specie.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged.

Drawings

The drawings in this application have been accepted. No further action by Applicant is required.

Information Disclosure Statement

The information disclosure statements filed 4/29/2004, 10/27/2004, 12/8/2006 have been considered. Initialed copies are enclosed.

The information disclosure statement filed 3/21/2005 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the information disclosure statement does have a column that provides a space, next to each document to be considered for the examiner's initials.

The above information disclosure statements have been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including

all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C (1).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1,2,3 and 22-25 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claim is drawn to a composition comprising an immunostimulatory nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 1.

The claimed invention is drawn to a product of nature. Products of nature are not patentable because they do not reflect the "hand of man" in the production of the product or manufacturing process. The recitation of isolated

immunostimulatory nucleic acid molecule in the claim will reflect the hand of man in said claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39 and 44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not reasonably provide enablement for a composition comprising the immunostimulatory nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 1 for treating or preventing an infectious disease or herpes simplex virus.

The claims are drawn to a composition comprising an immunostimulatory nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 1, wherein the immunostimulatory nucleic acid is provided in an amount effective to treat or prevent an infectious disease and effective to treat or prevent herpes simplex virus.

The scope of infectious disease is broad and includes diseases caused by a wide variety of viruses, fungi, bacteria and parasites (Mechanisms of Microbial Diseases 3rd edition, edited by Moselio et al. 1999, p. XV-XVI).

The nature of the invention and the scope of the claim is also drawn to the use of an immunostimulatory nucleic acid comprising SEQ ID NO: 1 to treat or prevent the broad scope of infectious disease as set forth supra.

Also, the scope of immunostimulatory nucleic acids include both those that are methylated and unmethylated.

The specification teaches and provides guidance as to the in vitro ability of SEQ ID NO: 1 (ODN 10103) to stimulate human PBMC p. 90. Pages 91,94 and 97 teach experiments examining the potential of SEQ ID NO: 1 to enhance antigen specific immune responses to hepatitis B surface antigen (HbsAg). CpG ODN 10103 significantly enhances antibody titers against HbsAg when administered together with HbsAg. A similar ODN CpG ODN 7909 was equally potent in enhancing antibody responses against HbsAg Ag when administered together with HbsAg Ag. Cytotoxic lymphocyte responses in animals immunized with HbsAg using ODN 10103 (SEQ ID NO: 1) appear to be greater than those induced by CpG ODN 7909.

The specification does not provide guidance to the treatment or prevention of any infectious disease using an immunostimulatory nucleic acid comprising SEQ ID NO: 1 by itself. No guidance is provided regarding the efficacy of said immunostimulatory nucleic acid by itself or compositions comprising said immunostimulatory nucleic acid in the treatment or prevention any infectious disease including herpes simplex virus. The specification does not correlate the clearing of infection e.g. herpes simplex virus with the administration of effective amounts of said immunostimulatory nucleic acid or compositions comprising such.

The state of the art at the time the invention was made teaches that immunostimulatory adjuvants such as CpG DNA activate cells of the innate immune system which in turn drive and focus the acquired immune response (to antigen) (see abstract of Hogan et al. Biomol Eng. 2001 18(3): 69-85). Immunostimulatory CpG nucleic acids have acted as adjuvants for antigenic vaccines against rotavirus and herpes simplex virus (Choi et al. Vaccine (2002) 20:1733-1740 and Gallichan et al. The Journal of Immunology (2001), 166 (5): 3451-3457). Gallichan et al teaches that mice immunized intranasally with herpes simplex virus antigen plus unmethylated CpG ODN used as adjuvant were significantly protected following intravaginal herpes simplex virus antigen (see abstract, p. 3451, right column second full sentence). Also, immunostimulatory nucleic acids do not prevent disease caused by herpes simplex virus as evidenced by fig. 7 (p. 3455) of Gallichan et al wherein unmethylated CpG ODN administered with antigen before challenge does not prevent the initial occurrence of virus shedding in mice subsequently immunized with virus.

Immunostimulatory nucleic acids comprising unmethylated CpG dinucleotide when administered alone protect against infection with lethal *L. monocytogenes* or *M. tuberculosis* in a mice model

(Juffermans et al. Infection and Immunity, Jan. 2002, p. 147-152, Krieg et al. Abstract presented at the 1996 meeting on Molecular Approaches to the Control of Infectious Diseases, Sept. 9-Sept. 13, 1996). However, said nucleic acids do not prevent disease due to said infectious organisms as Juffermans et al teach that mycobacterial infection and inflammation occurred in said immunized mice (see abstract p. 147, fig.1 p. 148 and fig.3 p. 149). As to prevention of a viral infection such as HIV in humans, prevention is currently geared towards prevention of mother to child transmission of the virus using antiviral drugs. In human adults, there are no preventative vaccines or drugs for HIV infection and therapeutic methods are geared to existing infection.

Unmethylated CpG ODN administered alone in a rodent malaria model conferred sterile protection against rodent malaria antigen challenge (Gramzinski et al. Infection and Immunity, Mar. 2001, p. 1643-1649). However, CpG ODN did not prevent malaria infection.

Although the state of the art at time of filing showed the efficaciousness of immunostimulatory nucleic acids such as CpG ODN (in animal models) in treating herpes simplex virus disease when used as an adjuvant in combination with antigen, treatment

of disease due to infection by Listeria, mycobacteria and malaria when used alone, the art does not teach prevention of these and other infectious diseases. The art and specification does not correlate treatment and prevention of all infectious diseases with any immunostimulatory nucleic acid (or compositions thereof).

All of the art cited above were performed in animal models and it is art recognized that for any novel therapy, the transition from the laboratory to the clinic (Petri dish experiments to animal experiments to bedside) is a quantum leap (Chatterjee et al. Cancer Immunol. Immunother., 1994, 38:75-82). Results obtained under controlled conditions and in inbred animals often differ from the clinical response obtained in patients. Since the therapeutic indices of immunotherapeutic regimens can be species and model dependent it is not clear that results obtained from animal data accurately reflects the efficacy of immunostimulatory nucleic acids (and compositions thereof) in humans. Furthermore, major considerations for any nucleic acid therapy protocol involve issues such as the amount of oligonucleotide administered, what amount is considered therapeutically effective, the route and time course of administration, sites of administration. For example, Gura

(Science vol. 270 p. 575-577, 1995, see p. 576 right column) teach that synthetic oligonucleotides have caused side effects in experimental animals and that when administered by one-time injection in high does, several phosphorothioates drugs were lethal to some of the animals. Furthermore, the oligonucleotides caused a transient decrease in two kinds of white blood cells as well as changes in blood pressure and heart rate. Such cardiovascular and other effects seen in animals can be minimized in patients using low does of the compounds and administering then gradually by continuous intravenous injection. Phosphorothioates have been found to accumulate in the liver, kidneys, and bone marrow of animals, although the long-term effects of this deposition are not clear (Gura).

Furthermore, the above applications for treatment of the stated infectious disease use immunostimulatory CpG ODN different from the instantly claimed SEQ ID NO: 1. Weiner et al (J. leukocyte biology 2000, 68: 455-463) teaches that all CpG ODN are not alike, and more needs to be learned about the heterogeneous responses that occur based on host organism, cell subset, or CpG ODN sequence. Ballas et al (J. Immunol. 2002, 168: 1212-1218) teaches that the selection of optimal CpG ODN, for example, in the case of cancer immunotherapy depends upon a careful analysis

of the cellular specificities of various CpG motifs and an understanding of the cellular mechanisms responsible for the antitumor activity in a particular tumor (abstract). Ballas et al teaches that a single CpG ODN cannot be used to treat all cancers and tumors.

Agrawal et al (TRENDS in Molecular Medicine, 2002, 8/3:114-120) also teaches that different effects are observed with different CpG ODNs.

It is therefore not clear that the skilled artisan could predict the efficacy of compositions comprising immunostimulatory nucleic acid comprising the nucleotide sequence of SESQ ID NO:1 in treating and preventing all types of infectious diseases and for treating and preventing herpes simplex virus due to the considerations set forth above. One of skill in the art would have to perform undue experimentation to test said oligonucleotides in different animal models representing the plethora of infectious organism causing infectious disease to determine whether the instantly claimed immunostimulatory nucleic acid (and composition thereof) is efficacious as claimed. Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary, the absence of working examples, the

nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention. The specification must have been enabling at the time the invention was made and developments after the time of filing are of no consequence to what one skilled in the art would have believed at the time of filing (In re Wright, 27 USPQ2d 1510).

Claim Rejections - 35 USC § 102 and 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference

is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 22-25 and 34-35 are rejected under 35 U.S.C. 102(e) as being anticipated by Olek et al. WO 2002/00926 A published Jan 3 2002 filed on June 29, 2001.

Claims 1, 22-25 and 34-35 are directed to a composition comprising an immunostimulatory nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 1, wherein immunostimulatory nucleic acid molecule includes at least four CpG motifs, wherein said nucleic acid is T-rich, wherein said nucleic acid includes a poly-T- sequence, wherein said nucleic acid includes a poly-G- sequence.

Olek et al teach a composition comprising SEQ ID NO:74 which comprises a nucleic acid comprising the instantly claimed nucleotide sequence of SEQ ID NO:1 (See attached sequence print out and sequence listing from Olek et al,p.7 second to the last paragraph and last sentence p. 8). Said immunostimulatory nucleic acids includes 4 CpG motifs, is T rich, includes a poly T sequence (TTTTT and TTTT) and includes a poly G sequence (GG). Since the nucleic acid comprising SEQ ID NO:1 of Olek et al and the instantly claimed nucleic acid is the same, said nucleic acid of Olek et al is also immunostimulatory and stimulates a mucosal, systemic and innate immune response absent evidence to the contrary.

Claims 1, 3-13, 16-38 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Olek et al. WO 2002/00926 A. published Jan 3 2002 filed on June 29, 2001 in view of Krieg et al. WO 2001/22972 A2, April 2001.

The claims are drawn to a composition comprising an immunostimulatory nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 1 further comprising an antigen.

Olek et al teach a composition comprising SEQ ID NO:74 which comprises a nucleic acid comprising the instantly claimed

nucleotide sequence of SEQ ID NO:1 (See attached sequence print out and sequence listing from Olek et al,p.7 second to the last paragraph and last sentence p. 8). Said immunostimulatory nucleic acids includes 4 CpG motifs, is T rich, includes a poly T sequence (TTTTT and TTTT) and includes a poly G sequence (GG). Since the nucleic acid comprising SEQ ID NO:1 of Olek et al and the instantly claimed nucleic acid is the same, said nucleic acid of Olek et al is also immunostimulatory and stimulates a mucosal, systemic and innate immune response absent evidence to the contrary.

Olek et al does not teach said composition further comprising an antigen a microbial antigen or a viral antigen or adjuvants or cytokines or antimicrobial agent (anti-viral). Olek et al does not teach nucleotide backbone modification of said immunostimulatory nucleic acid (phosphorothioate, chimeric) and does not teach said composition further comprising a pharmaceutically acceptable carrier. Olek et al does not teach said immunostimulatory nucleic acid free of unmethylated CpG dinucleotides, does not teach said nucleic acid formulated for oral,local, parenteral, mucosal administration or formulated in a sustained release device such as a microparticle. Olek et al

does not teach effective amounts of said composition for stimulating systemic or innate or mucosal immune responses

Krieg et al teach compositions of T rich immunostimulatory nucleic acids comprising poly T nucleic acids or compositions comprising immunostimulatory nucleic acids comprising 5'TCGTCGTT 3'or TG nucleic acids further comprising a microbial antigen such as a viral antigen or a peptide antigen (p. 60 lines 16-20, p. 62 line 18-21, p. 66 line 14, p. 157 claim 3, p.166 claim 103). Krieg et al teach that said antigen can be encoded by a nucleic acid vector and that said antigens (encoded by nucleic acid vector) are separate from said immunostimulatory nucleic acid (p. 13 line 17-21, p. 79 line 27, p. 160 claim 38). Krieg teaches that immunostimulatory nucleic acids can be used with an antigen to mount an antigen specific immune response (p. 62 line 17-20). The compositions of Krieg et al comprising immunostimulatory nucleic acids further comprises an adjuvant e.g. a mucosal adjuvant (p. 94 lines 15- 25, p. 96 line 29). Krieg et al teach the benefits of adjuvants in that they stimulate the immune system (p. 94 line 29-32, p. 95 line 14, line 25, p.96 line 29). Krieg et al also each said compositions further comprising therapeutic agents such as cytokines to enhance the immune response (p. 94 line 15-16). Krieg et al teach said compositions

further comprising anti-microbial agents such as an anti viral agent (p. 86). Krieg et al teaches that such anti microbial agents are capable of killing or inhibiting infectious organisms (p. 86 line 2-3). Krieg et al teach said compositions comprising immunostimulatory nucleic acids having nucleotide backbone modifications including phosphorothioate modification (p. 36 lines 1-19). Krieg et al also teach heterogeneous (chimeric) nucleotide backbone (p.36 lines 20-25) and entirely modified nucleotide backbone (p. 37 line10-12). Krieg et al teach that such nucleotide backbone modifications stabilize said nucleic acids against in vivo degradation by nucleases and modified nucleic acids may show more stimulatory activity due to enhanced nuclease resistance, increased cellular uptake, increased protein binding (p. 35 lines 24-26, p. 36 line 17-19). Krieg et al teaches said immunostimulatory nucleic acids free of methylated CpG dinucleotide (p. 158 claim 23). Krieg et al teach that a nucleic acid containing at least one unmethylated CpG dinucleotide activates the immune system. (p. 32 lines 20-23). Krieg et al teach pharmaceutical preparations of said composition comprising immunostimulatory nucleic acids in pharmaceutically acceptable carriers (p. 21, p. 117 line 29-32, p.118) for administration to a subject. Krieg teaches that

immunostimulatory nucleic acids can be formulated for oral administration (p. 118 line 7-32), and formulated as a nutritional supplement e.g. capsule, pill or sublingual tablet (p. 163 claim 80). Said immunostimulatory nucleic acid can be administered locally, parenterally, formulated in a sustained release device such as a sustained release device, formulated for delivery to a mucosal surface selected from oral nasal, rectal, vaginal and ocular surface (p. 13 lines 7- 16, p. 166 claim 104). Krieg et al teaches that said compositions comprising said immunostimulatory nucleic acids can be provided in an effective amount for stimulating the mucosal, systemic and innate immune responses (p. 157 claim 1, p. 159 claims 33-35, p. 163 claim 77). Krieg et al teaches methods for determining therapeutically effective amounts of said compositions comprising said immunostimulatory nucleic acids (p. 117 line 18-28).

It would be prima facie obvious to one of ordinary skill in the art at the time the invention was made to include an antigen in the composition of Olek et al which comprises an immunostimulatory nucleic acids comprising a nucleotide sequence which is T rich, contains poly T, contains TG and 5'TCGTCGTT 3' as taught by Krieg et al, thus resulting in the instant invention with a reasonable expectation of success. The motivation to do so

is because Krieg et al teaches that immunostimulatory nucleic acids can be used with an antigen such as a viral antigen(e.g. encoded by a nucleic acid vector or a peptide antigen) to mount an antigen specific immune response and that said immunostimulatory nucleic acids act as adjuvants. One will also be motivated to add an adjuvant or cytokine to the composition of Olek et al because Krieg et al teach the benefits of adjuvants (e.g. a mucosal adjuvant) and cytokines in that they stimulate the immune system. One of skill in the art will be motivated to add a anti-microbial agent such as an antiviral to the composition of Olek et al comprising an immunostimulatory nucleic acid because Krieg et al teach compositions comprising immunostimulatory nucleic acids as set forth supra further comprising anti-microbial agents such as an anti viral agent and Krieg et al teaches that such anti microbial agents are capable of killing or inhibiting infectious organisms. It is also prima facie obvious to introduce nucleotide backbone modifications (e.g. phosphorothioate, chimeric backbone, entire modification of nucleotide backbone) in the immunostimulatory nucleic acid of Olek et al because Krieg teaches that such modifications stabilize said nucleic acids against in vivo degradation by nucleases and modified nucleic acids may show more

stimulatory activity due to enhanced nuclease resistance, increased cellular uptake, increased protein binding. It is also prima facie obvious to include in the composition of Olek et al, a pharmaceutically acceptable carrier because Krieg et al teaches compositions comprising immunostimulatory nucleic acid for oral (nutritional supplement, capsule, pill, tablet) local, parenteral, mucosal administration formulated in carriers (e.g. sustained release devices such as microparticle) which are pharmaceutically acceptable for said administration. It would have been prima facie obvious to one of skill in the art at the time the invention was made to unmethylate CpG dinucleotide(s) present in the immunostimulatory nucleic acid of Olek et al because Krieg et al teaches immunostimulatory nucleic acids free of methylated CpG dinucleotide and Krieg et al teach that a nucleic acid containing at least one unmethylated CpG dinucleotide activates the immune system.

It is prima facie obvious to one of skill in the art at the time of the invention to formulate effective amounts of the composition of Olek et al to stimulate mucosal, systemic or innate responses because Krieg et al teaches methods for determining effective amounts of compositions comprising immunostimulatory nucleic acids and that such methods are well

known in the art and within the capabilities of the ordinary skilled artisan.

Status of the Claims

Claims 1-13, 16-39, 43 and 44 are rejected. Claim 2 is free of the art.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Oluwatosin Ogunbiyi whose telephone number is 571-272-9939. The examiner can normally be reached on M-F 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Examiner Jeffery Siew can be reached on 571-272-0787.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Oluwatosin Ogunbiyi

Examiner

Art Unit 1645

PATRICIA A. DUFFY
PRIMARY EXAMINER